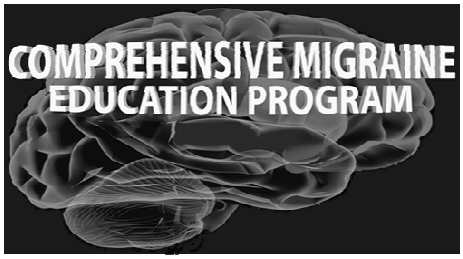

Preventive Treatment Strategies

Content developed by:
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AMERICAN HEADACHE SOCIETY
www.AmericanHeadacheSociety.org

COMPREHENSIVE MIGRAINE EDUCATION PROGRAM
www.AmericanHeadacheSociety.org

Faculty Disclosures

STEPHEN D. SILBERSTEIN, MD, FAHS
Dr. Silberstein has received consulting fees and/or honoraria from Allergan, Inc., Inc., Amgen, Avanir Pharmaceuticals, Inc., eNeura Inc, ElectroCore Medical LLC, Medscape, LLC, Medtronic, Inc, Mitsubhishi Tanabe Pharma America, Inc., Neuralieve; NINDS, Pfizer, Inc, Supernus Pharmaceuticals, Inc. and Teva Pharmaceuticals. His employer, Jefferson University Hospitals, receives research support from Allergan, Inc., Amgen, Cumberland Pharmaceuticals, Inc, ElectroCore Medical, LLC, Labrys Biologic; Eli Lilly and Company, Merz Pharmaceuticals and Troy Healthcare.

Learning Objectives

At the end of this presentation, participants will be better able to:

- Discuss when migraine prevention should be considered
- Identify the principles and objectives of therapy for migraine prevention
- Distinguish between medication overuse and medication overuse headache (MOH)
- Recall the factors that determine drug choice in migraine prevention
- Remember which evidence-based preventive migraine treatments are currently supported by evidence from randomized, controlled clinical trials
- Educate patients about the rationale for migraine prevention and the options available for treatment

Nearly 40% of Patients Should be Offered or Considered for Migraine Preventive Therapy

Lipton RB et al. *Neurology*. 2007;68:343–349.

Goals of Preventive Treatment

Decrease
- Migraine days
- Headache days
- Intensity of symptoms
- Duration of attacks
- Disability

Improve
- Response to acute medications
- Functional ability

Prevent disease progression

Benefits occur over time

Silberstein SD. *Neurology*. 2000;55:754–762.

General Principles of Migraine Prevention

- Start with low dose and increase slowly
- Allow for an adequate trial (2–3 months)
- Monitor medication usage
  - Avoid overuse of acute medications
  - Limit/Eliminate interfering drugs
- Evaluate preventive therapy
  - Use calendar/diary
  - Taper/discontinue if well-controlled at 6 months

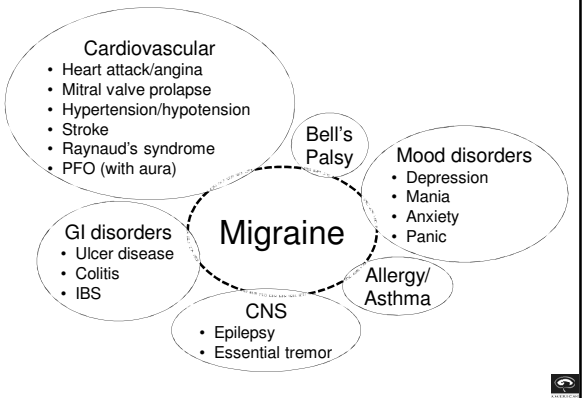
Silberstein SD. *Neurology*. 2000;55(6):754-762; Diener HC et al. *J Neurol*. 2004;251:943–950.

General Principles of Migraine Prevention *cont.*

- Manage communications
  - Ask about patient preference
  - Discuss contraception
- Optimize medication use
  - Best efficacy
  - Fewest AEs

Silberstein SD. *Neurology.* 2000;55(6):754-762; Diener HC et al. *J Neurol.* 2004;251:943–950.

Consider Comorbid Conditions



Consider Prevention When. . .

- Significantly interferes with routine activities despite use of acute treatment
- Attack frequency exceeds 1 per week
- Elevated risk of:
  - Medication overuse
  - Chronic Daily Headache

Consider Prevention When. . .*cont.*

- Acute medications
  - Ineffective
  - Contraindicated
  - Troublesome AEs
  - Overused
- Patients express/acknowledge a preference
- Uncommon migraine subtypes are present
  - Hemiplegic
  - Basilar
  - Prolonged Aura
  - Migrainous Infarction

Lifestyle Modifications

- Inquire about sleep disturbances/sleep hygiene
  - Avoid too little sleep, daytime naps
  - Avoid oversleeping in the morning
- Explain how to avoid excessive fatigue by pacing activities during the day/week
- Reduce and manage stress
- Encourage regular meals and exercise
- Behavioral therapy

Spierings EL et al. *Headache.* 2001;41:554–558.

Behavioral Therapy for Episodic and Chronic Migraine

Relaxation training, biofeedback, or both

Cognitive behavioral therapy

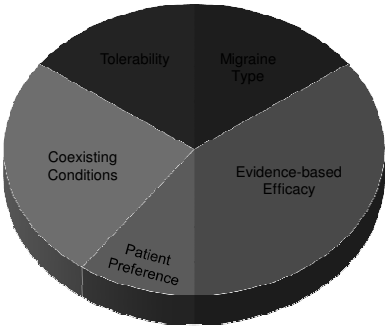
Benefits may include:

- Reduction in headache severity, frequency, and headache-related disability
- Reduction in reliance on drugs
- Enhanced HRQoL and sense of control

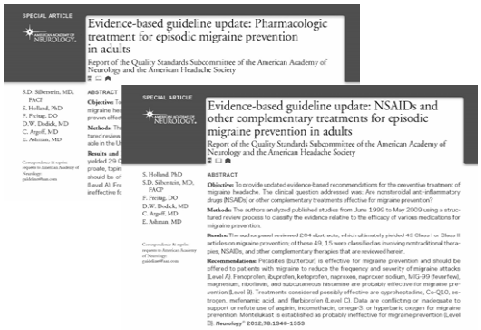
Afternoon session focused on behavioral therapy

Lipchik GL, Nash GM. *Curr Pain Headache Rep.* 2002;6:473–479.; Silberstein SD. *Neurology.* 2000;55:754–762.; Steiner TJ et al. *J Headache Pain.* 2007;8(suppl 1):S3–S47.

Factors in Preventive Drug Selection



Evidence-based Guidelines for Prevention of Migraine


SPECIAL ARTICLE

Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults

Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society

S.D. Silberstein, MD, FACP
S. Holland, PhD
F. Freitag, DO
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SPECIAL ARTICLE

Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults

Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society

S. Holland, PhD
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ABSTRACT

Objective: To provide updated evidence-based recommendations for the preventive treatment of migraine headache. The clinical question addressed was: Are nonsteroidal anti-inflammatory drugs (NSAIDs) or other complementary treatments effective for migraine prevention?

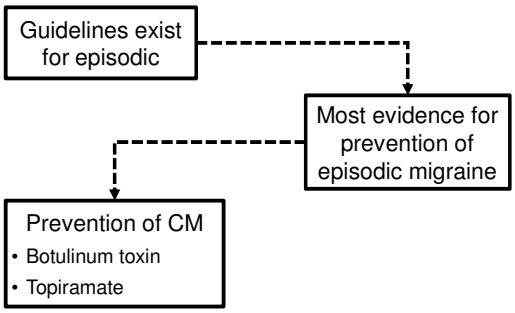
Methods: The authors analyzed published studies from June 1996 to Mar 2009 using a structured review process to classify the evidence relative to the efficacy of various medications for migraine prevention.

Results: The medical panel reviewed 254 short-term, ethics-approved pivotal RS (Class I or Class II artifacts) on migraine prevention; of these 89.1% were classifiable, involving nontraditional therapies, NSAIDs, and other complementary therapies that are reviewed herein.

Recommendations: Petasites (butterbur) is effective for migraine prevention and should be offered to patients with migraine to reduce the frequency and severity of migraine attacks (Level A). Feverfew, ibuprofen, ketoprofen, naproxen, naproxen sodium, MIG-99 (feverfew), magnesium, riboflavin, and acupuncture (manner and protocol unknown) are probably effective for migraine prevention (Level B). Treatments considered possibly effective are cyproheptadine, CoQ10, estrogen, mefenamic acid, and flurbiprofen (Level C). Data are conflicting or inadequate to support or refute use of aspirin, butterbur, omega-3, or hyperbaric oxygen for migraine prevention. Montelukast is established as probably ineffective for migraine prevention (Level B). *Neurology*® 2012;78:1346–1353

Silberstein SD et al. *Neurology.* 2012;78:1337-1345.; Holland S et al. *Neurology.* 2012;78:1346-1353.

Evidence of Efficacy



Preventive Therapies: Level A

Established as effective and should be offered for migraine prevention

- Divalproex sodium
- Sodium valproate
- Topiramate
- Metoprolol
- Cognitive Behavioral Therapy
- Propranolol
- Timolol
- Butterbur
- Biofeedback
- Relaxation Training

Silberstein SD et al. *Neurology.* 2012;78:1337-1345.
Dawn to send reference

Preventive Therapies: Level B

Probably effective and should be considered for migraine prevention

- Amitriptyline
- Venlafaxine
- Atenolol
- Nadolol
- NSAIDs
  - Fenoprofen
  - Ibuprofen
  - Ketoprofen
  - Naproxen
- Riboflavin
- Magnesium
- Mig 99 (feverfew extract)
- Histamine (subcutaneous)

Silberstein SD et al. *Neurology.* 2012;78:1337-1345.; Holland S et al. *Neurology.* 2012;78:1346-1353.

Preventive Therapies: Level C

Possibly effective and may be considered for migraine prevention

- Lisinopril
- Candesartan
- Clonidine
- Guanfacine
- Carbamazepine
- Nebivolol
- Pindolol
- Flurbiprofen
- Mefenamic acid
- Co-Q10
- Estrogen
- Cyprohepatadine

Silberstein SD et al. *Neurology*. 2012;78:1337-1345.; Holland S et al. *Neurology*. 2012;78:1346-1353.

Preventive Therapies: Level U

Evidence is conflicting or inadequate to support or refute use for migraine prevention

- Gabapentin
- Fluoxetine
- Fluvoxamine
- Protriptyline
- Acenocoumarol
- Coumadin
- Picotamide
- Bisoprolol
- Nicardipine
- Nifedipine
- Nimodipine
- Verapamil
- Acetazolamide
- Cyclandelate
- Aspirin
- Indomethacin
- Omega 3
- Hyperbaric oxygen

Silberstein SD et al. *Neurology*. 2012;78:1337-1345.; Holland S et al. *Neurology*. 2012;78:1346-1353.

Preventive Therapies: Level A, B, and C Negative

Level	Guidance for migraine prevention	Agent
A Negative	Ineffective; should not be offered	Lamotrigine
B Negative	Probably ineffective; should not be considered	Clomipramine Montelukast
C Negative	Possibly ineffective; may not be considered	Acebutolol Clonazepam Nabumetone Oxcarbazepine Telmisartan

Silberstein SD et al. *Neurology*. 2012;78:1337-1345.; Holland S et al. *Neurology*. 2012;78:1346-1353.

Evidence-based Preventive Therapies: Limitations and Opportunities

Medication	Contraindication(s)	Coexisting condition(s)
Anticonvulsants		
Divalproex sodium	• Liver disease • Bleeding disorders • Pregnancy (Category X)	• Mania • Epilepsy • Anxiety
Topiramate	• Kidney stones	• Epilepsy • Mania • Obesity
Antidepressants		
TCAs	• Mania • Urinary retention • Heart block	• Other pain disorders • Depression • Anxiety • Insomnia
SNRIs	• Mania	• Depression

TCA, Tricyclic antidepressants; SNRI, serotonin-norepinephrine reuptake inhibitor

Evidence-based Preventive Therapies: Limitation and Opportunities *cont.*

Medication	Contraindication(s)	Coexisting condition(s)
Beta blockers		
• Metoprolol • Propranolol • Timolol	• Asthma • Depression • CHF • Raynaud's • Diabetes	• Hypertension • Angina
Calcium channel blockers		
• Verapamil (with aura)	• Constipation • Hypotension	• Migraine with aura • Hypertension • Angina
NSAIDs		
• Ibuprofen • Naproxen	• Ulcer disease • Gastritis	• Arthritis • Other pain disorders
Complementary		
• Riboflavin • Co-Q10 • Petasites • Butterbur		• Preference for natural products

Preventive Treatment ARS Question 1

All of the following are general principles in migraine prevention except:

A. Discuss contraception
B. Consider comorbid conditions
C. Allow for a 1-month trial
D. Low initial dose, titrate slowly

Prevention of Chronic Migraine (CM)

General Principles in CM Prevention

Principle	Additional considerations
Individualize medication selection	Few patients: • Receive preventive therapy • Comply with treatment within first 3 months • Continue treatment for 1 year
Consider comorbid and coexistent illness/disorders	Maximize therapeutic opportunities • Choose a single drug for both conditions when possible • Combine preventive drugs in appropriate cases

Dodick DW, Silberstein SD. *Pract Neurol.* 2007;7:383–393.; Katsarava Z et al. *Curr Neurol Neurosci Rep.* 2009;9115–119.

General Principles in CM Prevention *cont.*

Select Medicines Based on Evidence in CM

Treatment	Evidence
Anticonvulsants	
Topiramate Gabapentin Valproate	• Double-blind placebo-controlled trials in CM • One double-blind, placebo-controlled trial in chronic daily headache • Small placebo-controlled and comparator trials in CM
Antidepressants	
Amitriptyline Fluoxetine Tizanidine	• Small open-label trial in transformed migraine • Small double-blind, placebo-controlled trial in chronic daily headache • Small double-blind, placebo-controlled trial in chronic daily headache (adjunctive)
Neurotoxins	
OnabotulinumtoxinA*	Double-blind placebo-controlled trials in CM

*FDA approved for CM

General Principles in CM Prevention *cont.*

Medication Overuse

- Overuse of acute medication is common
- 50%–80% of CM patients seen in headache clinics overuse acute medications
- Not all CM patients overuse medications
- Important clinical distinction:
  - Activity: overuse of medications
  - Disorder: Medication Overuse Headache (MOH)

Bigal RB, Lipton RB. *Neurology*. 2008;71;1821-1828.; Lipton RB, Bigal ME. *Neurology*. 2003;61;154-155.

ICHD-III β MOH

New Diagnostic Criteria

A. Headache* ≥15 days/month in a patient with pre-existing headache disorder

B. Regular overuse for >3 months of ≥1 acute/symptomatic treatment

1. Ergotamine, triptans, opioids, or combination analgesic medications on ≥10 days/month
2. Simple analgesics or any combination of ergotamine, triptans, analgesics, or opioids on ≥15 days/month on a regular basis without overuse of any single class alone

*If attributed to substance withdrawal, sub-classify as caffeine withdrawal headache; opioid withdrawal headache; estrogen withdrawal headache

Headache Classification Subcommittee of the IHS. ICHD-III (beta). *Cephalalgia*. 2013;33:629–808.

Comparing MOH with CM

MOH

A. Headache* ≥15 days/month in a patient with pre-existing headache disorder

B. Regular overuse for >3 months of ≥1 acute/symptomatic treatment

1. Ergotamine, triptans, opioids, or combination analgesic medications on ≥10 days/month
2. Simple analgesics or any combination of ergotamine, triptans, analgesics, or opioids on ≥15 days/month on a regular basis without overuse of any single class alone

CM

A. Headache (tension-type-like and/or migraine-like) on 15 days/month for >3 months

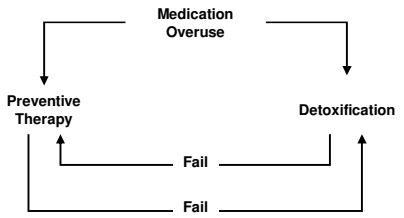
B. Patient has had ≥5 attacks fulfilling criteria for migraine with and/or without aura

C. On 8 days/month for >3 months, attacks fulfilling criteria for migraine with or without aura or believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

CM and MOH can co-exist

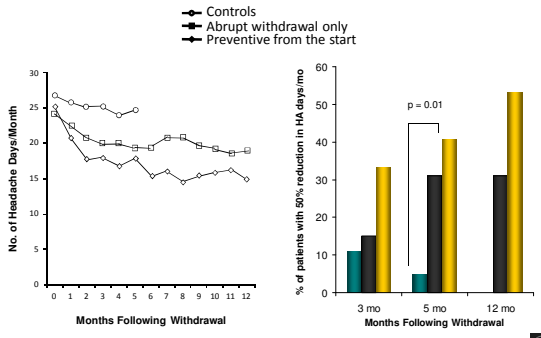
Headache Classification Subcommittee of the IHS. ICHD-III (beta). *Cephalalgia*. 2013;33:629–808.

Treatment of MOH



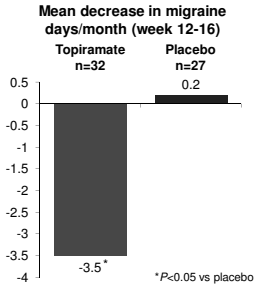
Bigal RB et al . *Neurology.* 2008;71;1821–1828.; Diener HC et al. *Lancet Neurol.* 2004;3:475–483.; Hagen K et al. *Cephalalgia.* 2009;29:221–232.

Better Long-term Outcomes in MOH with Preventive Treatment Plus Withdrawal



Hagen K et al. *Cephalalgia.* 2009;29:221–232.

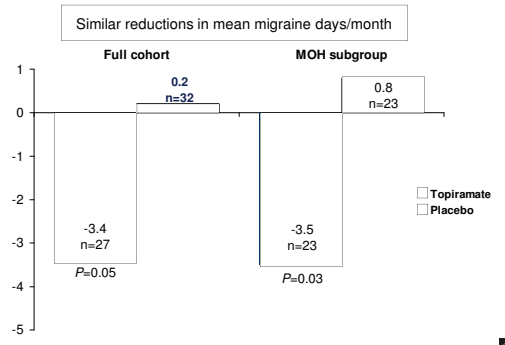
Topiramate Reduces Migraine Days in CM



- Treatments
  - Topiramate 100 mg/day (50–200 mg/day allowed)
  - Placebo
- Subjects: 78% met the definition for acute medication overuse at baseline

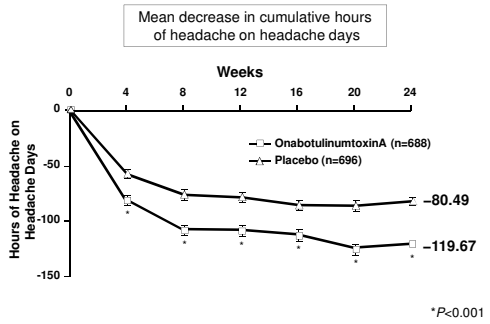
Diener HC *et al. Cephalalgia.* 2007;27:814–823.

Topiramate is Effective in CM Patients with or without Medication Overuse



Diener HC *et al. Cephalalgia.* 2007;27:814–823.

OnabotulinumtoxinA Significantly Outperforms Placebo from 4–24 Weeks in CM



Dodick DW, *et al. Headache.* 2010;50:921–936.

OnabotulinumtoxinA: Pooled Efficacy at Week 24

Mean Change From Baseline	Onabotulinum-toxinA (n=688)	Placebo (n=696)	*P*-value
Frequency of headache days*	-8.4	-6.6	<0.001
Frequency of migraine days	-8.2	-6.2	<0.001
Frequency of moderate/severe headache days	-7.7	-5.8	<0.001
Cumulative headache hours on headache days	-119.7	-80.5	<0.001
% Patients with severe (≥60) HIT-6 score	67.6	78.2	<0.001
Frequency of headache episodes	-5.2	-4.9	0.009
Frequency of migraine episodes	-4.9	-4.5	0.004
Frequency of acute headache medication intake	-10.1	-9.4	0.247

*Primary Measure

Dodick DW, *et al. Headache.* 2010;50:921-936.

Preventive Treatment ARS Question 2

At least _____% of CM patients seen in headache clinics overuse acute medications.

A. 30
B. 50
C. 78
D. 90

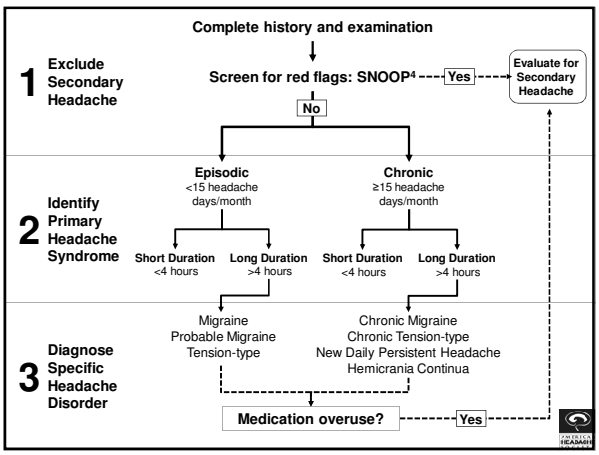
What's New in Migraine Prevention?

CGRP Monoclonal Antibodies

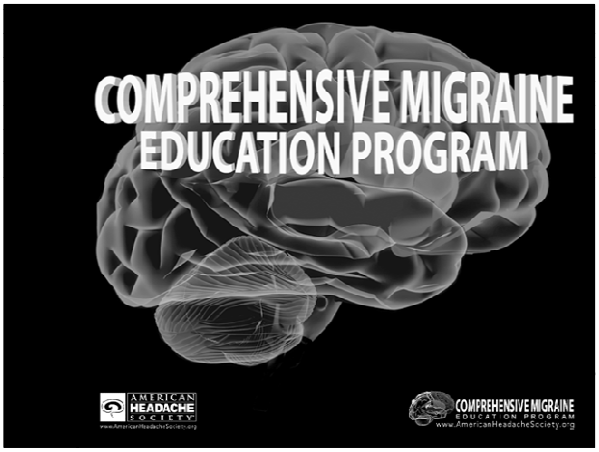
- Inhibition of neurogenic vasodilation with a long duration of action
- Skin vasodilation or increase in MMA diameter similar to CGRP receptor antagonists but slower onset
- Inhibition still evident one week after dosing
- Chronic treatment: no detectable effects on heart rate or blood pressure

Neurostimulation

- Nerves
  - Vagal
  - Frontal
- Transcranial magnetic stimulation
- Sphenopalatine ganglion stimulation



Summary

The most important aspects of the preventive treatment of migraine include:

- Accurate diagnosis
- Nonpharmacotherapy
  - Trigger management
  - Lifestyle modification
  - Behavioral therapy
- Use of symptomatic and prophylactic medications
- Management of medication overuse
- Monitor response to treatment: Diary, HIT-6, MSQOL
- Meaningful communication with/education of patients